UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,451	08/21/2003	Sydney Brenner	55525-8038.US01	9556

22918 7590 12/16/2005

PERKINS COIE LLP
P.O. BOX 2168
MENLO PARK, CA 94026

EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/646,451	BRENNER, SYDNEY	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 9-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9-16 is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 21 August 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the international Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: printout of NEBcutter restriction enzyme sites from GenBank Accession N. U02427.

DETAILED ACTION

Specification

1. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

2. On pages 11 and 12 of the specification "NACTA**C**" should read "NACTA**G**" because the BclI restriction site is ACTA**G**T.

Claim Objections

3. Claim 16 is objected to because of the following informalities:

In claim 16, "with said stuffer fragment" should read "within said stuffer fragment.

Priority

4. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120 or 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, a petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. However, Applicant is still required to submit the reference in compliance with 37 CFR

1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

In particular, the first line of the specification should be amended to recite, for example: This application is a divisional of U.S. Application 09/786,254, filed April 30, 2001, now U.S. Patent No. 6,653,077, which is the National Stage of International Application PCT/US99/20047, filed August 31, 1999, which claims the benefit of U.S. Provisional Application 60/099,147, filed September 4, 1998.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Miki (U.S. Patent NO. 5,595,895).

Miki (see, e.g., col. 10, lines 60-67 to col. 11 line 2; col. 16, lines 2-28) discloses a modified lambdaGem™11 cloning vector for incorporation of a DNA restriction fragment wherein the vector comprises a restriction enzyme recognition site, a stuffer fragment (also referred to as a multiple cloning site fragment) and a second restriction endonuclease recognition site. In particular, Miki teaches a cloning vector comprising a stuffer fragment flanked on each side by a restriction endonuclease recognition site for SfiI (a type II restriction endonuclease). With respect to claim 11, it is a property of the lambdaGem™11 cloning vector of Miki that it contains, in addition to the stuffer

fragment, a first and a second restriction endonuclease site selected from the group of sites of SapI, EarI and HinfI.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hung (Nucleic Acids Research. 1984. 12: 1863-1874) in view of Miki.

Hung (Figure 1 and pages 1865-1866) teaches methods for cloning a restriction fragment wherein the methods comprise:

providing a population of restriction fragments, each having a recessed 3' strand and a protruding 5' strand;

extending the 3' recessed strand by one nucleotide to form a modified end (see page 1870, Figure 3; "(i)in the insert DNA, a single nucleotide was filled into the Sal I generated ends");

providing a vector comprising a first and a second type II restriction endonuclease (i.e., XbaI);

digesting the cloning vector with the first and second type II restriction endonuclease to form an opened vector;

inserting the restriction fragments having modified ends into the opened vector; and

transforming host cells with the cloning vector carrying the inserted restriction fragment.

Hung does not specifically teach that the cloning vector comprises a "stuffer fragment."

However, Miki teaches methods for cloning a population of restriction fragments into a vector wherein the restriction fragments and vector have been modified by partially filling-in the 3' recessed strand of the restriction fragment (see col. 10, lines 27-43). Miki (col. 13) teaches that the cloning vector comprises a "stuffer fragment" containing at least 2 restriction enzyme sites. Cleavage of the cloning vector with the restriction enzymes releases the stuffer fragment, allowing one to distinguish between vectors comprising the stuffer fragment (open vectors) and un-digested vectors that still contain the stuffer fragment.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hung so as to have used a cloning vector containing a stuffer fragment in order to have achieved the benefits of providing a vector that contained restriction sites that would allow for the insertion of the DNA fragments and of providing a vector that would allow one to distinguish between fully digested/opened vectors and undigested vectors, thereby increasing the overall efficiency and applicability of the cloning method.

7. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung in view of Miki and further in view of Bellemare (Gene. 1990. 101: 67-74).

The teachings of Hung are presented above. In particular, Hung (page 1866) teaches that the 3' recessed strand of the DNA fragment is partially filled in using reverse transcriptase. Hung (page 1866) states that "(w)e assume that the large proteolytic fragment of *E. coli* DNA polymerase I can also be used for this filling reaction. However, Hung does not specifically exemplify filling in the 3' recessed strand using a DNA polymerase.

Bellemare (see, e.g., abstract) teaches using the Klenow fragment of *E. coli* DNA polymerase I to partially fill in 3' recessed strands of DNA restriction fragments. Bellemare (page 68) teaches that the partial filling-in procedure can be achieved with PolIK (i.e., the Klenow fragment of *E. coil* DNA polymerase), T4 DNA polymerase or reverse transcriptase.

In view of the teachings of Bellemare, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hung so as to have used the Klenow fragment of *E. coli* DNA polymerase in place of reverse transcriptase because this would have provided an equally effective means for filling in the 3' recessed strands of the DNA restriction fragments.

With respect to claim 14, Hung teaches that the 5' protruding end consists of 4 nucleotides (see, e.g., page 1872, Figure 1).

8. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung in view of Miki and Bellemare and further in view of Xu (U.S. Patent No. 5,663,067).

The teachings of Hung, Miki and Bellemare are presented above. The combined references do not teach digesting the cloning vector with the restriction enzyme Sap I.

However, Hung teaches that a variety of distinct restriction enzymes can be used in the cloning method and specifically states that "(m)any different sticky ends can be made complementary by filling part of their sticky ends." Hung teaches the process of how to select appropriate restriction enzymes for the DNA fragment and the selection of nucleotides for filling in recessed 3' strands in order to generate termini which do not self-ligate or form concatamers but which allow for the insertion of a modified DNA restriction fragment into a cloning vector. Further, Bellemare extends these studies and provides a wide variety of type II restriction endonucleases, including 4 and 6 cutter restriction endonucleases, which can be used to generate cohesive-ends for cloning DNA fragments into cloning vectors (see Tables 1 and 2). Bellemare also provides the general guidelines for selecting compatible restriction enzymes for cleaving the DNA fragments and the cloning vector.

Miki teaches methods for cloning a DNA fragment into a cloning vector wherein the DNA fragment is modified by partial filling-in of the recessed 3' strand and the cloning vector is digested with a restriction enzyme that generates overhangs that are not complementary and therefore will not self-ligate (see, col. 8, 9 and 13). Miki also teaches that the cloning vectors contain a stuffer fragment that includes the 2 restriction enzyme sites for a type II restriction enzyme that cleave at nonsymmetrical recognition sites to generate non-complementary overhangs (see, e.g., col. 13). Miki teaches that

any restriction enzyme that cleaves at a nonsymmetrical recognition site to generate non-complementary overhangs can be used to digest the cloning vector.

Xu teaches the Sap I type II restriction endonuclease and the recognition sequence that is cleaved by this endonuclease (see, e.g., paragraph 17). Xu teaches that the recognition site for Sap I is asymmetric and consists of the sequence of:

5'...GCTCTTC$(N)_1$...3'

3'...CGAGAAG$(N)_4$...5's

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Hung so as to have used Sap I to digest the cloning vector, rather than using the particular restriction enzymes exemplified by Hung (see Figure 1) in order to have provided a method in which DNA restriction fragments modified to have partially filled-in ends complementary to the ends generated by Sap I could be effectively ligated into the cloning vector. Further, in view of the teachings of Miki, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a cloning vector containing two Sap I sites in the stuffer fragment of the cloning vector because cleavage of the two Sap I sites would have resulted in the removal of the stuffer fragment and would have generated con-complementary overhangs, thereby preventing self-ligation of the vector. Given the teachings of Hung and Bellemare regarding the strategies for generating sticky ends that would allow for ligation of modified DNA fragments into cloning vectors, while preventing self-ligation of the DNA fragments, and the teachings of Miki of the use of cloning vectors containing a stuffer fragment that includes 2 type II restriction

endonuclease sites that generate overhangs that are not complementary, the selection of alternative restriction enzymes for digesting the cloning vector, including the selection of Sap I, would have been obvious to one of ordinary skill in the art and well within the skill in the art at the time the invention was made.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A. NCBI Database, GenBank Accession No. U02427 and U02426, discloses the right and left arm of the cloning vector lambda EMBL3 SP6/T7.

B. The Promega Catalog, available via the Internet at <URL: promega.com/vectors/lambda/vectors.htm> discloses that the LambdaGem-11 cloning vector consists of the sequences of the right arm (GenBank Accession No. U02427) and the left arm (GenBank Accession No. U02426).

C. The New England BioLabs web site, NEBcutter, (available via the Internet at <URL: tools.neb.com/NEBcutter2/index.php> provides a list of each of the restriction enzyme sites present in the right arm of the lambdaGem™11 cloning vector, including a EarI site at position 44, a SapI site at positions 44 and 382 and a HinfI site at positions 76 and 214.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach

the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
November 29, 2005

CARLA J. MYERS
PRIMARY EXAMINER